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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,866	07/02/2002	Michael Schirner	SCH 1869	6769

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EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	**PAPER NUMBER**
1643	

MAIL DATE	DELIVERY MODE
11/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,866	SCHIRNER ET AL.	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed on 11/6/07 has been considered. Applicant's arguments are deemed to be persuasive-in-part.

Claims 15-35 are pending.

The new matter rejection and the objection to specification is withdrawn in view of applicant's arguments.

The art rejections are withdrawn and re-written.

The issue of common ownership is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 16, 18, 20, 22, 27-33 and 35 remain/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 18, 20, 22 and 27-33 were inadvertently omitted from the previous office action. Claim 35 is added because of its recitation of L19. The reasons for this rejection are of record in the paper mailed 2/1/06.

Applicant argues that the Pini et al reference states that the reference in Table II states that the sequences were deposited in the EBI database and that one skilled in

the art could use the CITEEXPLORE program and retrieve all the information relating to those accession numbers. First of all, the sequences in the table provided by applicant shows on single chains. Applicant is claiming the entire antibody. The table says nothing about the constant regions. Second, the table states "recombinant antibody, partial". It is not clear what this means. Third, deposit information needs to be in the specification. Applicant is cautioned against the addition of the deposit information of EBI into the specification as it would be new matter.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 15, 17, 19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al Nature Biotechnology Vol. 15 p. 1271 (11/97) as evidenced by Milton US 6342326.

This reference discloses making and using scFv(CGS-1) labeled with infrared fluorophore Cy7 and the use of this antibody-dye conjugate to detect blood vessels and to image tumors (reads on using in a pharmaceutical composition) in tumors by fluoresce microscopy (see page 1272 and 1273). ScFv is directed to ED-B fibronectin, which as is also known as oncofetal fibronectin (see abstract). It is inherent that the conjugate "accumulates in the edge area of the cell tissue of a focus of disease" making the edge area of the focus of disease optically detectable. Since Cy7 is the same dye used by applicant, it is inherent that the visible or near-infrared light induce the fluorescent intensity.

Milton discloses the structure of Cy7 (see figure 1 top right) and this reads on applicant's compounds when D is radical III and B is formula VIII (referring to claim 1 of the instant invention).

Claims 15-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al US 2003/0045681 (filed 5/11/98) as evidenced by Milton US 6342326.

This reference discloses making and using scFv(L19) labeled with infrared fluorophore Cy5 and the use of this antibody-dye conjugate to detect and image newly formed blood vessels (reads on using in a pharmaceutical composition) and this reference also discloses conjugates using scFvE1 instead of L19 (see [0036]-[0037], [0042], [0072], Examples 2-6). It is inherent that the conjugate "accumulates in the edge area of the cell tissue of a focus of disease" making the edge area of the focus of

disease optically detectable. Since Cy5 is the same dye used by applicant, it is inherent that the visible or near-infrared light induce the fluorescent intensity.

Milton discloses the structure of Cy5 (see figure 1 top left) and this reads on applicant's compounds when D is radical III and B is formula VI (referring to claim 1 of the instant invention).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al Nature Biotechnology Vol. 15 p. 1271 (11/97) or Neri et al US 2003/0045681 (filed 5/11/98) in view of Viti et al Cancer Research vol. 59 p. 347 (1/99), applicant's admission in the sentence bridging pages 7-8 of the specification and Licha et al US 6083485 (filed 11/7/97).

Both Neri et al references have been discussed above.

The only difference between the instant invention and the reference is the different cyanine dyes, the use during surgery (intropeative) and the use of L19 or E1.

Viti et al discloses that antibody L19 and E1 can be used in vivo to target new forming blood vessels of F9 teratocarcimona(page 349 (second column)) and that these antibodies have increased binding affinity (last sentence in abstract).

Licha et al disclose a protein-dye conjugate wherein the dye is "F" (col. 4-5) and the a cyanine dye of the formula IIa. This formula reads on applicant's formula in claim 15. The dyes of this reference are irradiated with light from the visible to near infrared range from 650-1200 nm (see abstract and claims and column 8, lines 42-50). This

reference also discloses the injection of these compounds into small body cavities or small blood or lymph vessels (col. 9, lines 39-52) (this reads on intraoperative methods or "during surgery") for in vivo diagnostic procedures. Furthermore, this reference discloses that the use of cyanine dyes shows 1000 times greater fluorescent intensity and that the compounds overcome the problems of cyanine dyes because they have little protein affinity (problems such as low fluorescent intensities due to aggregation) (see col. 13, lines 15-25 and col. 9, lines 25-30).

Additionally in the sentence bridging pages 7-8 of the specification, applicant admits that "both macroscopic and microscopic detection are possible" using dyes in the near infrared range.

Since Licha et al discloses protein-dye conjugates using cyanine dyes and the use of these dyes in small body cavities or small blood or lymph vessels (reads on during surgery and intraoperative) and since the cyanine dyes of the reference have increased fluorescent intensity and overcome some of the problems associated with cyanine dyes, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the dyes of the secondary reference in place of the dyes of the primary reference with the expected benefit of achieving a conjugate that can be used in vivo diagnostic assays and with the expected benefit that the conjugate "accumulates in the edge area of the cell tissue of a focus of disease" making the edge area of the focus of disease optically detectable and with the ultimate expected result of achieving a conjugate with increased fluorescent intensity. In view of the fact that L19 and E1 can target newly formed blood vessels (reads on the edge area) in vivo and

have increased binding affinity, it also would have been obvious to use L19 or E1 in the conjugate of the primary reference with the expected benefit of achieving an antibody-dye conjugate with higher binding affinity. Since both macroscopic and microscopic detection are possible using dyes in the near infrared range it also would have been obvious to use either detection method when using the protein-dye conjugates.

Response to applicant's arguments

Applicant provides a declaration showing unexpected results. Applicant's arguments to the previous action are accepted. Applicant's showing of unexpected results are not accepted for the following reasons: (1) it is not clear if the antibody used in all 5 conjugates is the same or different. (2) the showing of increased fluorescence is not really unexpected because as stated in Licha et al the cyanine dyes of this reference have 1000 times greater fluorescent intensity and that the compounds overcome the problems of cyanine dyes because they have little protein affinity (problems such as low fluorescent intensities due to aggregation) (see col. 13, lines 15-25 and col. 9, lines 25-30). Thus, one of ordinary skill in the art would expect to see an increased signal. (3) With respect to the increased immunoreactivity, one of ordinary skill in the art would expect this because Viti et al states that these antibodies do have increased binding affinity (last sentence in abstract).

Claims 15-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al Nature Biotechnology Vol. 15 p. 1271 (11/97) or Neri et al US 2003/0045681

(filed 5/11/98) in view of Viti et al Cancer Research vol. 59 p. 347 (1/99), applicant's admission in the sentence bridging pages 7-8 of the specification and Licha et al US 6083485 (filed 11/7/97) and Licha et al 6630570 (filed 4/12/99). The reasons for this rejection are of record in the paper mailed 6/22/06.

Neri et al, Neri et al, Viti et al, Licha '485 and applicant's admission have been discussed above.

The only difference between the instant invention and the reference is the different cyanine dyes.

Licha et al disclose a protein-dye conjugate wherein the dye is "F" (col. 4-5) and the a cyanine dye of the formula IIa. This formula reads on applicant's formula in claim 15. The dyes of this reference are irradiated with light from the visible to near infrared range from 650-1200 nm (see abstract and claims and column 8, lines 42-50). This reference also discloses the use of conjugates in intraoperative procedures (ie during surgery (col. 18, lines 33-53). This reference also specifically discloses the dyr of claim 34 (see legend of figure 1).

Additionally in the sentence bridging pages 7-8 of the specification, applicant admits that "both macroscopic and microscopic detection are possible" using dyes in the near infrared range.

Since Licha et al discloses protein-dye conjugates using cyanine dyes and the use of these dyes in small body cavities or small blood or lymph vessels (reads on during surgery and intraoperative) and since the cyanine dyes of the reference have increased fluorescent intensity and overcome some of the problems associated with

cyanine dyes, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the dyes of the secondary reference in place of the dyes of the primary reference with the expected benefit of achieving a conjugate that can be used in vivo diagnostic assays and with the expected benefit that the conjugate "accumulates in the edge area of the cell tissue of a focus of disease" making the edge area of the focus of disease optically detectable and with the ultimate expected result of achieving a conjugate with increased fluorescent intensity. Because the conjugate would specifically bind to newly formed vessels and not pre-existing ones, this reads on recognizing the edge of the vessel. In view of the fact that L19 and E1 can target newly formed blood vessels (reads on the edge area) in vivo and have increased binding affinity, it also would have been obvious to use L19 or E1 in the conjugate of the primary reference with the expected benefit of achieving an antibody-dye conjugate with higher binding affinity. Since both macroscopic and microscopic detection are possible using dyes in the near infrared range it also would have been obvious to use either detection method when using the protein-dye conjugates.

Response to applicant's arguments

Applicant provides a declaration showing unexpected results. Applicant's arguments to the previous action are accepted. Applicant's showing of unexpected results are not accepted for the following reasons: (1) it is not clear if the antibody used in all 5 conjugates is the same or different. (2) the showing of increased fluorescence is not really unexpected because as stated in Licha et al US 6630570 the cyanine dyes of

this reference are expected to yield a highly sensitive, detectable fluorescence signal (col. 2, lines 4-5). Thus, one of ordinary skill in the art would expect to see an increased signal. (3) with respect to the increased immunoreactivity, one of ordinary skill in the art would expect this because Viti et al states that these antiboides do have increased binding affinity (see rejection).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesday and Thursday from 5:30am to 1:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sheela J Huff
Primary Examiner
Art Unit 1643

sjh